## REMARKS

Claims 9 and 11-24 are pending as of the mailing date of the Advisory Action of April 12, 2005. According to the Advisory Action, the Amendment of March 28, 2005 has been entered, the new matter rejection relating to the specification has been withdrawn, and the objection to claim 10 has been withdrawn.

**Advisory Action of 12 April 2005**

The Examiner asserted in the Advisory action that the statements provided in the Amendment and Reply to Final Office Action dated 28 March 2005 could not place the application in condition for allowance because "[a]ttorney argument is not evidence unless it is an admission." In support of this assertion, the Examiner cited MPEP § 2145 and MPEP § 716.01(c). The Examiner also cited *In re Geisler*, 116 F.3d 1465 (Fed. Cir. 1997) for the proposition that "[a]n assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness," and *In re Schulze*, 346 F.2d 600, 602 (CCPA 1965) for the proposition that "arguments of counsel cannot take the place of evidence in the record."

Applicant respectfully disagrees with the Examiner that Applicant's Amendment and Reply of 28 March 2005 could not place the application in condition for allowance. Applicant submits that Applicant is not required to present an affidavit or declaration to overcome the Examiner's rejections. In contrast, the MPEP explicitly states that

> [o]bjective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

MPEP § 716.01(c)(I) (*see also*, MPEP § 716.01(c)(II)). The statements in the Amendment and Reply of 28 March 2005 were not offered for the reasons enumerated in the above-cited section of the MPEP. In contrast, the statements were offered in reply to written description and enablement rejections interposed by the Examiner. Accordingly, Applicant submits that MPEP § 716.01(c)(I) should not be applied here.

Applicant submits that the Examiner's reliance on MPEP § 2145 is similarly inappropriate for rejecting the statements in the Amendment and Reply of 28 March 2005. MPEP § 2145 enumerates the following arguments that should be supported by declaratory evidence: (1) arguments about additional advantages or latent properties; (2) arguments that prior art devices are not physically compatible; (3) arguments against references; (4) arguments about the number of references combined; (5) arguments about limitations that are not claimed; (6) arguments regarding economic infeasibility; (7) arguments about the age of references; (8) arguments that prior art is nonanalogous; and (9) arguments regarding inappropriateness of combining references. MPEP 2145. In contrast, Applicant's statements in the 28 March 2005 Amendment and Reply address none of the situations enumerated in MPEP 2145. Accordingly, Applicant submits that MPEP § 2145 should not be applied.

But regardless of whether or not MPEP 2145 or 716.01(c) could be properly applied, Applicant submits that the statements made in the Amendment and Reply of 28 March 2005 are supported by evidence in the record and not solely by attorney argument—namely, by the references cited and submitted in information disclosure statements in this application. Applicant has not merely asserted that Applicant was in possession of the invention as of the filing date, and has not merely asserted that the claims are enabled to a person of ordinary skill in the art. Rather, Applicant has provided objective evidence—in the form of references cited and disclosed in information disclosure statements—that address the Examiner's rejections. Applicant's statements were supported by references cited and supplied in information disclosure statements submitted in this application. Applicant submits that the

allegedly insufficient statements pointed the Examiner to objective evidence present in the cited publications that pre-date the priority date of the instant application. Applicant submits that the Examiner has not articulated a reason why the Examiner discounted the references cited by Applicant in the Amendment and Reply of 28 March 2005, which references reflect the level of ordinary skill in the art before the priority date of the instant application with respect to the allegedly non-enabled subject matter and with respect to the subject matter allegedly non-compliant with the written description requirement. Accordingly, Applicant submits that sufficient objective evidence has been provided by Applicant in response to the Examiner's written description and enablement rejections and thus no declaration or affidavit is required.

**Rejections Under 35 U.S.C. § 112, First Paragraph: Written Description**

Claim 9 and 11-23 stand rejected as allegedly failing to satisfy the written description requirement, asserting that the disclosure fails to provide an adequate written description of how the claimed methods are to be performed. The Examiner asserted that none of the examples in the specification are drawn to the claimed methods, indicating that the claims include performing the methods *in vivo*, and asserting that introducing RNA having the structure $X_1$-L-$X_2$ into any cell and having such transfection result in the desired end product is most difficult and unpredictable.

The Examiner also asserted that the ability to selectively and effectively target the correct target gene is critical, and that the specification is essentially silent as to what the target genes are and how to identify a suitable gene as compared to an unsuitable gene. Further, the Examiner asserted that the specification does not disclose how to perform the methods for any and all life forms, including humans.

The claims have been amended in the Amendment and Reply of 28 March 2005 to recite that the method is carried out *in vitro*, and to remove reference to performing the claimed methods in an organism. Applicant submits that the amendments overcome the

Examiner's written description rejections regarding *in vivo* application of the claimed methods. The Examiner's remaining objections are addressed below.

Applicant refers the Examiner to arguments previously made of record in Applicant's response filed 27 September 2004 and 28 March 2005, and Applicant respectfully disagrees with the Examiner's written description rejections. The written description requirement is satisfied when an application describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). But the disclosure as originally filed does not need to provide *in haec verba* support for the claimed subject matter at issue. *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320 (Fed Cir. 2000) (citation omitted). Rather, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question. *Fujikawa v. Wattanasin*, 93 F.3d 1559 (Fed. Cir. 1996). If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the written description requirement is met; the Examiner's burden is to provide reasons why a person of ordinary skill in the art would not consider the description sufficient. *In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996).

Applicant submits that the Examiner has not established why a person of ordinary skill in the art would not consider the description sufficient with regard to introducing, *in vitro*, an RNA having the structure $X_1$-L-$X_2$ into a cell other than the cells disclosed in the specification, and having the transfection result in inhibition of an RNA. No reason has been articulated as to why a person of ordinary skill in the art would doubt that RNA comprising the structure $X_1$-L-$X_2$ could be transfected into any cell type known in the art that is capable of being transfected *in vitro* with a nucleic acid. Transfecting cells with nucleic acids was well known in the art at the time of filing. Accordingly, any alleged failure to describe transfection conditions in detail should not support a written description rejection.

Further, Applicant has adequately described how the A549 cells used to illustrate the claimed methods were transfected. See, for example, the specification as filed at page 14, second full paragraph. Examples of other disclosures of transfecting cells with nucleic acids are provided below.

Yu *et al.* (2002) *PNAS* 99/9:6047-6052 (Yu), cited previously against the claims by the Examiner, discloses transfection into mouse P19 cells (see, for example, Yu at page 6047, column 2, lines 8-10) of vectors coding for hairpin RNAs. Further, Yu indicates that transfection was performed by a method known in the art (see, for example, Yu at page 6048, paragraph straddling columns 1 and 2).

Piccin *et al.* (2001) *Nucleic Acids Res.* 29/12 e55:1-5 (Piccin), submitted herewith in an information disclosure statement, also discloses introducing a transgene encoding for a hairpin RNA into *Drosophila melanogaster* P19 cells (see, for example, Piccin at page 2, col. 1, first sentence of first full paragraph, and page 1443, col. 2, final paragraph).

Holen *et al.* (2002) *Nucleic Acids Res.* 30/8:1757-1766 (Holen), submitted herewith in a supplemental information disclosure statement, discloses introducing siRNA (chemically synthesized 21-23 bp double stranded short interfering RNAs) into HeLa, Cos-1, and 293 cells (see, for example, Holen at page 1758, left column, first two full paragraphs).

Caplen *et al.* (2001) *Proc. Natl. Acad. Sci. USA* 98/17:9742-9747 (Caplen), submitted herewith in a supplemental information disclosure statement, discloses introducing siRNAs (chemically synthesized 21-25 nt double stranded RNAs) into HeLa cells, primary mouse embryonic fibroblasts, and 293 cells (human kidney) (see, for example, Caplen at page 9743, left column, first full paragraph).

These references establish that introducing nucleic acids into cells, in particular for performing RNA interference, was well known in the art before the priority date of the instant application. Accordingly, Applicant submits that a person of ordinary skill would have understood the inventor to have been in possession of the claimed invention at the time of filing.

Applicant also respectfully disagrees that the written description requirement is not met because the application allegedly does not disclose how to identify a target gene or suitable gene and how to selectively and effectively target the gene. Methods for selecting hairpin RNA that are capable of inhibiting a target mRNA were known in the art at the time the application was filed. Examples of disclosures published before the priority date of the instant application that describe how hairpin RNAs are selected with respect to their targets are provided below. In light of these references, a person of ordinary skill in the art would readily appreciate that the inventors were in possession of the claimed invention at the time the application was filed.

Yu discloses that hairpin siRNAs can effectively inhibit RNAs that are complementary to either the sense or antisense siRNAs (see, for example, Yu at page 6049, col. 2, final paragraph) to achieve RNA interference.

The Examiner is also referred to Piccin, which also shows transfection of a construct that gives rise to a hairpin RNA effective in performing RNA interference. Piccin discloses that "[i]ntroduction of double-stranded RNA (dsRNA) triggers degradation of the mRNA bearing the same sequence in a variety of organisms," and discloses a transgene that gives rise to a hairpin siRNA within a cell following transfection.

The Examiner is also referred to Holen and to Caplen, cited above in response to the written description rejections and provided herewith in a supplemental information disclosure statement. Both Holen and Caplen establish that, before the filing date of the instant

application, it was known in the art how to select a sequence for an interfering RNA molecule that would exhibit at least some functionality as a silencing agent.

The cited references establish that it was known in the art before the filing date that RNA sequences in RNAs, such as those designated $X_1$ and $X_2$ of the present claims, can be selected by making $X_1$ or $X_2$ complementary to the mRNA to be inhibited. Accordingly, the written description requirement is satisfied and no reasonable basis exists to doubt that a person of ordinary skill in the art would find the disclosure sufficient.

**Rejections Under 35 U.S.C. § 112, First Paragraph: Enablement**

Claims 9 and 11-23 stand rejected as allegedly failing to comply with the enablement requirement. The Examiner asserted that none of the intended utilities have been fully enabled by the specification, including gene therapy or identification of a gene as a suitable target for drug development. The Examiner also asserted that the specification does not include the requisite starting materials and reaction conditions that would permit a person of ordinary skill in the art to reproducibly manufacture any and all useful interfering hairpin RNA molecules, asserting that the methods of claims 9 and 11-23 encompass gene therapy in any individual, including a human. Further, the Examiner asserted that the specification is silent as to what mRNA sequences are to be used and how they are to be introduced into any subject to selectively diminish mRNA transcription without resulting in toxicity to a cell/individual.

Applicant has amended the claims to recite that the method is carried out *in vitro*. Reference to using the method in an organism in claim 10 has been addressed in the Amendment and Reply of 28 March 2005 by canceling claim 10 and adding claim 24, which omits reference to carrying out the method in an organism. Applicant submits that the amendments to the claims overcome the Examiner's enablement rejections, and Applicant addresses the Examiner's rejections in relation to the claims below to the extent that the Examiner may apply the rejections to the claims.

The Examiner is referred to arguments in support of the claims previously made of record in Applicant's responses of 27 September 2004 and 28 March 2005. The Examiner is also referred to arguments made above in connection with Applicant's response to the Examiner's written description rejections.

To satisfy the enablement requirement, the claimed invention must be enabled so that a person of skill in the art could make and use the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The test is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. *U.S. v. Telectronics, Inc.,* 857 F.2d 778, 785 (Fed. Cir. 1988). In determining whether the enablement requirement is satisfied, it is to be noted that a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner,* 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), *cert. denied,* 480 U.S. 947 (1987). To state a *prima facie* enablement rejection, an Examiner must establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright,* 999 F.2d 1557, 1562 (Fed. Cir. 1999).

Applicant submits that the Examiner has not provided a reasonable basis to doubt the objective truth of the statements in the specification that teach how carry out the methods of the amended claims. In particular, Applicant submits that no reasonable basis is articulated to doubt the objective truth of the teaching contained in page 8, line 26 to page 9, line 34;page 12, line 21 to page 13, line 27; and page 14, line 22 to page 15, line 13 as to making the exemplary RNAs, and paragraphs page 10, lines 1 to 27; page 14, lines 4 to 18; and page 15, lines 2-13 as to using the exemplary RNAs, and the Figures. Thus, the specification fully enables methods for inhibiting a target mRNA *in vitro* in accordance with the amended claims.

Further, Applicant submits that claim 24 added by the Amendment and Reply of 28 March 2005, corresponding to canceled claim 10, is enabled. Claim 24 recites that the method is carried out *in vitro*, and omits reference to carrying out the method in an organism. Accordingly, claim 24 includes assaying *in vitro* whether a gene product is a suitable target for drug discovery. Applicant refers the Examiner to the arguments made above regarding selection of $X_1$ and $X_2$ sequences directed against a target gene. Applicant submits that the method of claim 24 can be employed using a hairpin RNA against any coding region of a genome. If inhibiting the mRNA of a target gene results in an effect in the cell, that is, results in a measurable phenotype, then the product of the target gene can be a target for drug discovery, wherein drug discovery is aimed at producing the same measurable phenotype. See, for example, page 10, lines 12-19 of the application as filed.

Additionally, Applicant respectfully disagrees with the Examiner's arguments that this case is analogous to *Genentech v. Novo Nordisk* ("*Genentech*"). *Genentech* was decided on strikingly different facts. In *Genentech*, the claims recited a method for making human growth hormone in a fusion protein and cleaving the fusion protein to make the growth hormone. The patentees in *Genentech* tried to rely on the level of skill in the art to enable the claim, but at the time of filing the application it was ***not*** known in the art how to cleave a fusion protein to make growth hormone, ***where the cleaving of the fusion protein was the novel aspect of the claim***. In contrast, the novel aspect of the amended claims does not include novel methods for selecting nucleotide sequences against target mRNAs. As set forth above in Applicant's remarks regarding the written description rejections, methods of selecting sequences for hairpin RNAs that are at least active against a target mRNA were known in the art at the time the instant application was filed. Accordingly, Applicant submits that an enablement rejection of the amended claims predicated on an alleged lack of a discussion of how to select an RNA sequence for a hairpin RNA that is at least active against a target mRNA would be improper.

Accordingly, in light of the remarks above, Applicant requests reconsideration and

withdrawal of the written description and enablement rejections.

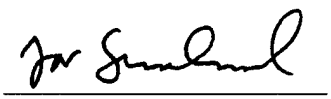
**Conclusion**

In view of the foregoing, reconsideration and allowance are respectfully solicited.

No fee is believed to be due with respect to the filing of this Reply other than the enclosed RCE fee. If any fees are due, or an overpayment has been made, please charge, or credit, Deposit Account No. 11-0171 for such sum.

If the Examiner has any questions regarding the present application, the Examiner is cordially invited to contact Applicant's attorney at the telephone number provided below.

Respectfully submitted,



Tor Smeland
Registration No.: 43,131
Attorney for Applicant

Kalow & Springut LLP
Telephone No.: (212) 813-1600